

Atty. Docket No. P58126US1

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:

Metin COLPAN et al.

Serial No.: 08/796,040

Group Art Unit: 1623

Filed: February 5, 1997

Examiner: L. Crane

For: DEVICE AND A PROCESS FOR THE ISOLATION OF NUCLEIC ACIDS

## RESPONSE

Commissioner of Patents  
Washington, D.C. 20231

Sir:

The instant paper responds to the Office Action mailed October 26, 2001.

Claims 101-119 are presented for consideration.

The instant Office Action represents a reopening of *ex parte* prosecution following Applicant's Brief on Appeal (filed July 2, 1999), the Examiner's Answer (mailed August 11, 1999), and Applicant's Reply Brief (filed October 12, 1999). The rejections and supporting reasoning contained in the instant Office Action are found in the Examiner's Answer. The instant Office Action contains arguments, not previously of record, directed against Applicant's remarks in the Brief on Appeal and Reply Brief, which arguments mis-characterize Applicant's remarks and are otherwise incorrect, to a large extent.

In the context of the maintaining the rejections as set forth in the Examiner's Answer, the instant Office Action contains arguments, not previously of record, directed against Applicant's

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remarks, (repeated below), which further arguments mis-characterize Applicant's remarks and are otherwise incorrect, to a large extent.

Claim 117 was rejected under 35 USC 112, ¶1, for allegedly lacking enablement with respect to the claim terminology "or mixture thereof." Reconsideration is requested.

According to the statement of rejection, the claim lacks enablement because it is broader in scope than "disclosed specific embodiments" in the specification (Office Action page ). This statement of rejection is incorrect. Lack of enablement under §112 is not established by mere allegations of undue breadth, that is, by merely arguing that claims read on non-disclosed embodiments. *Horton v. Stevens*, 7 USPQ2d 1245 (BPA & I 1988). In order to satisfy the requirements of §112, first paragraph, "it is not necessary to embrace in the claims or describe in the specification all possible forms in which the claimed principle may be reduced to practice." *Smith v. Snow*, 294 U.S. 1, 11 (1935). The law does not require an applicant to describe in his specification every conceivable embodiment of the invention. *SRI Int'l v. Matsushita Elec. Corp. of America*, 227 USPQ 577, 586 (Fed. Cir. 1985). Moreover, while working examples drawn to specific embodiments may be desirable, they are not *required* in order to satisfy enablement under §112. *In re Strahilevitz*, 212 USPQ 561 (CCPA 1982). Accordingly, the rejection under §112, ¶1, cannot be maintained.

The statement of rejection alleges that Applicant relies on the argument "that the term 'mixture thereof' was deleted from claim 117" (Office Action page 3). The allegation is incorrect. As explained in the Reply Brief (page 1):

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As a preliminary matter, the undersigned wishes to correct an inadvertent error made in Appellant's brief, filed July 2, 1999. At page 6 of Appellant's brief, under heading "B," addressing the rejection under 35 USC 112, 1<sup>st</sup> ¶, the statement appears: "Claim 117 does not recite 'mixture thereof,' the basis of the rejection (the term was deleted from corresponding appealed claim 79)." The foregoing quoted statement was made in error, by confusing claim 79 with claim 71, from which had been deleted "a combination thereof." Accordingly, the Examiner's Answer (at pages 5 and 6) is correct, in stating that claim 117 recites the term "or mixture thereof." The error, although inadvertent, is sincerely regretted.

The statement of rejection is also incorrect in alleging that "applicant makes no other argument" with respect to the §112, ¶1, rejection. The Examiner's attention is directed to the Reply Brief, page 2, in this respect.

Claims 117 and 118 were rejected under 35 USC 112, ¶2, for allegedly being indefinite for using the terms "includes" and "mixtures thereof," in claim 117, and the term "comprising," in claim 118. Reconsideration is requested.

With respect to the term "includes," use of the term in claim 117 is not indefinite. The claim recites the "solution *includes*" certain components. The statement of rejection maintains that

the term "includes" is incorrect as applied to a compound as said term is used as the equivalent of open language, e.g., --comprises--. Applicant is requested to note that claims directed to chemical compounds are indefinite when terms using variations of the verb "to comprise" or their verbal equivalents are included.

This may be all well and good when "claims directed to chemical compounds" are at issue. The problem is, the rejected claim is *not directed to a chemical compound*. Claim 117 is directed to a "process," not a chemical compound, and the term "includes" is not applied to a compound but, rather, to "an aqueous alcoholic solution." Since the reasoning set forth in the statement of rejection

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concerns matters irrelevant to the term "includes" as used in the context of the rejected claim, the rejection under §112, ¶2, based on use of the term cannot be maintained.

The § 112, 2<sup>nd</sup> paragraph, rejection of the terms "includes" is, moreover, unsupported by any reference to a statute, rule, regulation, or controlling case law. Applicant is free to be his own lexicographer. *In re Castaing*, 166 USPQ 550 (CCPA 1970). *In re Zletz*, 13 USPQ2d 1320 (Fed. Cir. 1989). It is the applicant's prerogative to define the claims, not the examiner's. *In re Pilkington*, 162 USPQ 145 (CCPA 1969).

Moreover, the indefiniteness rejection is based on the argument that "includes" leaves the claim open to non-recited elements and, as such, is concerned the scope of the claim, which concern is irrelevant to an inquiry under §112, ¶2. Claim "breadth is not to be equated with indefiniteness." *In re Miller*, 169 USPQ 597 (CCPA 1970).

With respect to the term "or mixture thereof," the rejection appears to be the result of misinterpreting the meaning of "or mixture thereof" in the context of the claim. Claim 117 limits "the aqueous alcoholic solution" in the parent claim to one which

includes from 1 to 7 M sodium perchlorate, from 1 to 7 M guanidine-HCl, from 1 to 5 M sodium chloride, from 1 to 6 M sodium iodide, and 1 M sodium chloride in 20% ethanol, propanol, isopropanol, butanol, poly(ethylene glycol), or mixture thereof.

Broken down to its component parts, first, the solution "includes from 1 to 7 M sodium perchlorate, from 1 to 7 M guanidine-HCl, from 1 to 5 M sodium chloride, from 1 to 6 M sodium iodide, and 1 M sodium chloride" (**emphasis added**), i.e., the solution must include **all** of 5 recited ingredients in their recited molar amounts. Secondly, all of the recited 5 ingredients in their recited molar

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amounts are "in 20% ethanol, propanol, isopropanol, butanol, poly(ethylene glycol), or mixture thereof," i.e., a limitation on the "alcoholic" part of "the aqueous alcoholic solution."

Mistakenly, the statement of rejection argues that "or mixture thereof" somehow refers to (i.e., modifies) the recited 5 ingredients in their recited molar amounts, which argument makes no sense. The recited 5 ingredients in their recited molar amounts must be present *together* by virtue of using the conjunctive *and*, i.e., the solution includes "from 1 to 7 M sodium perchlorate, from 1 to 7 M guanidine-HCl, from 1 to 5 M sodium chloride, from 1 to 6 M sodium iodide, *and* 1 M sodium chloride" (*emphasis added*). Since the 5 ingredients must be present, together, and must be present together "in 20% ethanol, propanol, isopropanol, butanol, poly(ethylene glycol), or mixture thereof" (*emphasis added*), there is no way "or mixture thereof" could refer to the 5 ingredients and make any sense.

The plain meaning of claim 117 is its proper interpretation. There is nothing ambiguous or confusing in the claim language. Claims are to be given their broadest reasonable interpretation during prosecution, but the definition of a claim limitation given by the Examiner cannot be different than would be given by one of ordinary skill in the art. *In re Cartright*, 49 USPQ2d 1464 (Fed. Cir. 1999).

When the applicant states the meaning that the claim terms are intended to have, the claims are examined with that meaning, in order to achieve a complete exploration of the applicant's invention and its relation to the prior art.

*In re Zletz*, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989).

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With respect to use of "comprising" in claim 118, the rejection cannot be maintained for the same reasons that the rejection based on "includes" cannot be maintained, as explained above.

The rejection with respect to "comprising" is based on "failure to further define the implied missing components of the buffer" (Office Action page 4). Thus, the rejection is based on the fact that use of "comprising" in claim 118 leaves the claim open to, i.e., it does not exclude, non-recited elements from the claims. Again, the statement of rejection concerns itself with claim scope, which has nothing to do with, and can not be used to support, a rejection under §112, ¶2, since claim "breadth is not to be equated with indefiniteness." *Miller, supra*.

The statement of rejection alleges that text in the Reply Brief "acknowledges that the rejections of record under 35 U.S.C. §112 have a proper basis and the examiner's allegations . . . have a reasonable basis in fact" (Office Action page 3). The statement of rejection is mistaken.

Quoting from the text at issue in the Reply Brief (*emphasis added*):

the Examiner's Answer (at pages 5 and 6) is **correct, in stating that claim 117 recites the term "or mixture thereof."** . . . [A]s relating to the term "or mixture thereof," both the rejections under 112, first paragraph, and 112, second paragraph, might be the result of the scope afforded to the term "mixture thereof" by the Examiner in interpreting the claim. That is, claim 117 limits "the aqueous alcoholic solution" to that which contains recited molar amounts of ingredients "in 20% ethanol, propanol, isopropanol, butanol, poly(ethylene glycol), *or mixture thereof*" (*emphasis added*). In other words, the term "mixture thereof" refers only to the recited "ethanol, propanol, isopropanol, butanol, [and] poly(ethylene glycol)," which comprise "20%" of "the aqueous *alcoholic* solution" (*emphasis added*) recited at the beginning of the claim. Therefore, the molar concentrations of "1 to 7 M sodium perchlorate, from 1 to 7 M guanidine-HCl, from 1 to 5 M sodium chloride, from 1 to 6 M sodium iodide, and 1 M sodium chloride" **are not modified by the term "mixture thereof."**

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Acknowledgment only that the term "or mixture thereof" is, in fact, in claim 117 in no way "acknowledges that the rejections of record have a proper basis and the examiner's allegations . . . have a reasonable basis in fact," as alleged in the statement of rejection. Moreover, stating that

the molar concentrations of "1 to 7 M sodium perchlorate, from 1 to 7 M guanidine-HCl, from 1 to 5 M sodium chloride, from 1 to 6 M sodium iodide, and 1 M sodium chloride" ***are not modified by the term "mixture thereof"***

(*emphasis added*) directly contradicts "that the rejections of record have a proper basis and the examiner's allegations . . . have a reasonable basis in fact."

Claims 101-119 were rejected under 35 USC 103 based on the combined teachings of Henco, Little, *International Dictionary of Medicine and Biology*, Vol. 1, 1986 (New York) page 522, and *Nucleic Acid Hybridisation - A Practical Approach*, 1985 (Washington D.C.) pages 64, 65, and 235 (Hames). Reconsideration is requested.

The rejection is fatally defective because reliance on Henco and Little is misplaced.

The process according to the instant claims saliently differs from Henco in that steps c) and d) of claim 101 are neither taught nor suggested. Henco contains no motivation to modify the process disclosed in therein by the steps c) and d) of present claim 101. No hint is given in Henco that (i) an increase in salt concentration should be effected in the sample fraction, nor is there any hint that (ii) such a fraction should be subsequently treated by application to a mineral support material in order to bind thereto the nucleic acid contained in the fraction, nor is there any hint to (iii) subsequently elute the substrate-bound nucleic acids using a buffer having very low ionic strength.

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Little provides no teaching or suggestion to supply the salient deficiencies in Henco. Almost the same distinction with Henco applies with regard to the distinguishing Little from the presently claimed process. Applicant could not find any passage in the whole disclosure of Little that nucleic acids, *which have already been separated*, should be subjected to a treatment according to the process of Little. Therefore, there is indeed no motivation to combine the two documents, either in modifying Little according to Henco or in modifying Henco according to Little; or that any motivation is provided in the art to look to Henco or Little as suggested by the statement of rejection.

Applicant respectfully submits that the combination of Henco and Little is overly simplistic. Again, Henco discloses purification of nucleic acids by an anion exchange treatment or an anion exchange separation process. The key features are binding the nucleic acid at low ionic strength and eluting the nucleic acids at concentrations in the range of 2 M salt in the buffer (the number can be derived from Fig. 4 of the specification of Henco). No use of any material for being a chaotropic salt is disclosed or suggested in Henco.

According to the statement of rejection, the "choice of a specific chaotropic agent to be included in an elution buffer is a variation in chromatographic procedure which statement of rejection asserts is clearly within the perview [*sic*] of the ordinary practitioner unless applicant has shown unexpected results" (Examiner's answer, page 13). The alleged "variation in chromatographic procedure" being within the knowledge "of the ordinary practitioner" merely points out that the skilled artisan would have known *how* to vary the chromatographic procedure taught in the prior art had the skilled artisan thought up the *idea* of doing so, in the first place. With all due



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respect, the statement of rejection's argument fails to take into account that *invention* comprises both the *idea* of the invention and the *means* to achieve that idea. *In re Cocer*, 175 USPQ 26 (CCPA 1972). Both the idea and means to achieve the idea must be evidenced in the prior art in order to demonstrate lack of patentability. *Id.* That a difference with the prior art amounts to an alleged "optimal condition" is "not a substitute for some teaching or suggestion supporting an obviousness rejection." *In re Rijckaert*, 28 USPQ 2d 1955, 1957 (Fed. Cir. 1993). Again, both the *idea* and the *means* to achieve the idea must be evidenced in the prior art in order to show obviousness. *In re Hoffman*, 37 USPQ 222 (CCPA 1938). "That which is within the capabilities of one skilled in the art is not synonymous with obviousness [citations omitted]. *Ex parte Levengood*, 28 USPQ 2d 1300, 1302 (Bd. Pat. App. & Inter. 1993). Whether or not Little accidentally uses a substance that happens to be, assuming arguendo, a chaotropic agent, but does not use it for that purpose, does not suggest use of the material as a chaotropic agent to one of ordinary skill in the art. *Minnesota Mining & Manufacturing Co., supra*.

On the other hand, Little binds nucleic acids from a solution having a very high content of salts, especially chaotropic salts.

The skilled artisan would not have had any incentive to even increase the "high" salt concentration obtained after Henco's process after reading Little's disclosure. That optional desalting is taught in Henco by the procedures disclosed therein is not disputed, but it fail to support the allegation that the skilled artisan would have been motivated to rely on Little's process in order to "desalt" Henco's sample. According to Henco, if desired, the skilled artisan would, regardless of the

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circumstance, try to reduce the salt content; either by applying a salt concentration, as low as possible, in the eluting step or by trying to desalt the sample by well known conservative methods, such as dialysis or gel permeation chromatography.

By no means however, would the skilled artisan ever consider, as opposed to getting rid of the salt, actually *increasing* after elution the salt content of the sample in Henco's process in order to obtain a sample having a very, very high salt concentration, as required in Little. The fact that, in accordance with the presently claimed invention, there is performed the step of increasing the salt content after Henco's process, in order to be able to employ process steps as disclosed in Little, may be regarded as a key unexpected step of steps as disclosed in the present invention.

The statement of rejection maintains that Little contains motivation to substitute the three desalting methods used in Henco (column 7, lines 44 to 46) with the silica separation method according to Little. The statement of rejection is mistaken.

Henco starts with DNA having a relatively low concentration of salt, which is not comparable with the situation Little addresses in the introductory portion of his disclosure. The DNA fractions dealt with in the paragraph cited by the statement of rejection are obtained after a cesium chloride gradient centrifugation. With respect to the samples which would be obtained in "too high a dilution," applicant submits that Henco teaches a method for separating DNA, wherein the DNA is not highly diluted in the eluate obtained from the method. Since the DNA is first absorbed on the chromatographic matrix and is afterwards desorbed in one elution step, the concentration of DNA is considerably high in the feral eluate. By analogy, therefore, Little's

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separation would be considered by the skilled person as an alternative *separation* method for isolating DNA; not as a mere substitute desalting step.

On the other hand, the method of the presently claimed invention utilizes, for the first time, the *effect* of silica disclosed in Little for such desalting steps. Originally, Little was not at all dealing with a desalting method, but with a separation method starting with highly concentrated salt solutions. This is evident from column 2, line 17 et seq. of Little, where it is stated: "This invention is directed to a process for the *purification* of plasmid and other DNA, both single-stranded and double-stranded, by immobilizing the DNA onto diatomaceous earth particles and eluting the DNA with water or low salt buffer (emphasis added)."

Therefore, the skilled artisan would not have considered using the procedure of Little as the optional desalting step of Henco. The argument made in the statement of rejection is a matter of hindsight; picking out features of the claimed process and trying to find the features in some piece of prior art. "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988). Little is not concerned in any way with desalting of a sample. Little is concerned with purification of DNA found in a high-salt solution. Henco, however, does not yield such a sample having nucleic acid in a high salt environment.

The statement of rejection takes out of context certain statements made in Little; which distorts what is, actually, described by the reference. That is, Little states "the invention is directed generally to the immobilization of DNA onto diatomaceous earth which comprises contacting the

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DNA with the diatomaceous earth in the presence of a chaotropic agent" (Little column 2, lines 32-35). Similar statements are made, elsewhere, in the reference. The statement of rejection characterizes these references in a manner that makes it *appear* as if Little encompasses (that is, *contemplated*) using *isolated* DNA as a *starting material*.

On the contrary, Little was concerned with the *desire* "to rapidly and inexpensively *separate* and purify DNA that was also amenable to scale-up" (Little column 1, lines 66-67). Little contemplated purifying DNA from "bacterial lysates" (Little column 1, lines 11-12); "plasmid DNA *from mini-prep lysates* can be purified using the process of the present invention" (Little column 5, lines 43-44), "this example illustrates that DNA can be purified *from bacterial lysates* independently of the method used to prepare the DNA and *without prior phenol extraction to remove proteins*" (Little, example 1) "the isolation of supercoiled DNA *from an agarose gel* by binding onto diatomaceous earth" (Little example 4), "nucleoside from triphosphates *are effectively removed from radiolabeling reactions* by the process of the present invention" (Little example 5), "the removal of linkers *from cloning reactions* using the process of the present invention" (Little example 6). Accordingly, Little contemplated, and described, a process that would address the problem whereby the "purification of plasmid DNA from bacterial lysates is a rate-limiting and time-consuming step in molecular biology" (Little column 1, lines 11-13), and fulfilled the objective whereby "a method was still desired *to rapidly and inexpensively* separate and purify DNA that was also amenable to scale-up" (Little column 1, lines 66-68).

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As a result, the desirability (that is, motivation) provided by Little was to develop a process for isolated and purifying DNA that was more *rapid* than known methods. This motivation would not have led one of ordinary skill in the art to combine Little with Henco since it would not have sped up the process of either Little or Henco, at all; in fact, it would have increased the time over and above that needed to perform either the Henco process or the Little process. If there were any motivation, it would have been to *replace* the Henco method, entirely, with the Little method; which, also, would have effected the optional *desalting* step taught by Henco.

The rejection uses impermissible *hindsight*; that is, by selectively picking and choosing from Little's teachings in a manner that fails to appreciate Little, as a whole.

It is impermissible within the framework of §103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.

*In re Hedges*, 228 USPQ 685, 687 (Fed. Cir. 1986).

Furthermore, the suggested combination would destroy the invention upon which Little was based; that is, for example, a *one*-step procedure to save time. A reference cannot be used (under § 103) to show obviousness in a manner that destroys the invention on which the reference is based.

*In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984).

The rejection, also, is fatally defective because reliance on *International Dictionary* and Hames is misplaced.

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*International Dictionary* and Harnes are relied upon to allegedly show that Henco describes the use of "chaotropic" salts and, therefore, is allegedly appropriately combined with the teachings of Little (cited in the statement of rejection) which teaches the binding of nucleic acids found in a solution having a high concentration of "chaotropic" salts. . . .

*International Dictionary* and Harnes add nothing to cure the fatal deficiencies found in the Henco and Little references . . . . The statement of rejection relies on the two newly cited references to allegedly show that materials disclosed in the previously cited prior art fall within the definition of "chaotropic agents." However, even assuming, arguendo, the statement of rejection is correct, the statement of rejection acknowledges that the "Henco reference does not make specific reference to a chaotropic agent." Whether or not, however, materials described by Henco accidentally fall within a broad definition of "chaotropic agent," Henco neither teaches nor suggests use of these materials for their allegedly *chaotropic* function. Therefore, even should the newly cited references show that materials described in the originally cited prior art fall within the definition of chaotropic agent, there remains no teaching or suggestion in the prior art for using these materials as chaotropic agents; and, the statement of rejection's argument that they might function as such provides no reason or motivation for one of ordinary skill in the art to combine the materials in the manner presently claimed. Claims do not read on the prior art if "chemicals, although present in the prior art, were used for other non- . . . [claimed] functions and did not [perform the claimed function] . . . as . . . understood from the . . . specification." *Minnesota Mining & Manufacturing Co. v. Johnson & Johnson Orthopaedics, Inc.*, 24 USPQ 2d 1321, 1327 (Fed. Cir. 1992).

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According to the statement of rejection, Applicant's arguments are not persuasive for failing "to provide a clear statement of how the combination of Henco et al. and Little has in any way destroyed the invention of Little as delineated by the claims found at the end of Little." The statement of rejection's reliance on the "claims found at the end of Little" as to what Little taught to one of ordinary skill in the art is misplaced. It is well-established that a patent's *claims* are no measure of what a patent discloses for prior art purposes of 35 U.S.C. 102 and 103. *In re Benno*, 226 USPQ 683 (Fed. Cir. 1985). Indeed, it is the teachings of Little, as a whole, not merely those of Little's claims that must be applied to the presently claimed invention for purposes of analysis under §103 of the statute.

The statement of rejection mischaracterizes Applicant's arguments as based on destroying "the motivation provided by Henco." Applicant made no argument about destroying "the motivation provided by Henco"; it is the motivation alleged by the statement of rejection to be found in the prior art, which Applicant disputes. It is the combined teachings of the prior art, taken as a whole, which must be considered in an obviousness analysis. *Ryko Manufacturing Co. v. Nu-Star, Inc.*, 21 USPQ 2d 1053 (Fed. Cir. 1991). Therefore, increasing the salt concentration in accordance with the teachings of Little is *not* "irrelevant to the question of motivation" to combine the prior art, contrary to the statement of rejection's argument.

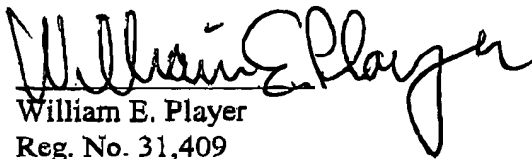
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Favorable action is requested.

Respectfully submitted,

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